STIC Search Report
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STIC Database Tracking Number: 137889

TO: Kevin Weddington **Location: rem/3a65/3c70** **Art Unit: 1614** **Wednesday, November 24, 2004** **Case Serial Number: 10/806088**	**From: Peggy Ruppel** **Location: Biotech-Chem Library** **REMSEN 1B65** **Phone: 571-272-2557** **Peggy.Ruppel@uspto.gov**

Search Notes

I limited the number of databases I searched because I found such good art so quickly.

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sira
Search and Information Resources Administration

REM-3C70

Access DB# 137889

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: K. Weddington Examiner #: 68082 Date: 11-15-04
Art Unit: 1614 Phone Number ~~30~~ 272-0587 Serial Number: 10/806,088
Mail Box and Bldg/Room Location: REM-3A65 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need. ME

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

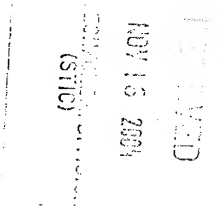
Inventors (please provide full names): _____

_____

Earliest Priority Filing Date: _____

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Treating cancer with (-) gossypol



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STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: _____	NA Sequence (#)_____	STN _____
Searcher Phone #: _____	AA Sequence (#)_____	Dialog _____
Searcher Location: _____	Structure (#) _____	Questel/Orbit: _____
Date Searcher Picked Up: 11-24-04	Bibliographic _____	Dr.Link _____
Date Completed: _____	Litigation _____	Lexis/Nexis _____
Searcher Prep & Review Time: _____	Fulltext _____	Sequence Systems _____
Clerical Prep Time: _____	Patent Family _____	WWW/Internet _____
Online Time _____	Other _____	Other (specify) _____

PTO-1590 (1-2000)

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=> b reg
FILE 'REGISTRY' ENTERED AT 13:26:52 ON 24 NOV 2004
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Property values tagged with IC are from the ZIC/VINITI data file
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STRUCTURE FILE UPDATES:   22 NOV 2004  HIGHEST RN 786612-66-6
DICTIONARY FILE UPDATES:  22 NOV 2004  HIGHEST RN 786612-66-6

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d que l1
L1            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "(-)-GOSSYPOL"/CN


=> d ide l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   90141-22-3  REGISTRY
CN   [2,2'-Binaphthalene]-8,8'-dicarboxaldehyde, 1,1',6,6',7,7'-hexahydroxy-
     3,3'-dimethyl-5,5'-bis(1-methylethyl)-, (2R)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   [2,2'-Binaphthalene]-8,8'-dicarboxaldehyde, 1,1',6,6',7,7'-hexahydroxy-
     3,3'-dimethyl-5,5'-bis(1-methylethyl)-, (R)-
OTHER NAMES:
CN   (-)-Gossypol
CN   (R)-(-)-Gossypol
CN   (R)-Gossypol
MF   C30 H30 O8
CI   COM
LC   STN Files:   AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS,
       CASREACT, IPA, MRCK*, NAPRALERT, PROMT, RTECS*, TOXCENTER, USPAT2,
       USPATFULL
         (*File contains numerically searchable property data)
DT.CA  CAplus document type:  Conference; Journal; Patent
RL.P   Roles from patents:  BIOL (Biological study); PREP (Preparation); USES
       (Uses)
RLD.P  Roles for non-specific derivatives from patents:  BIOL (Biological
       study); USES (Uses)
RL.NP  Roles from non-patents:  ANST (Analytical study); BIOL (Biological
       study); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP
       (Properties); RACT (Reactant or reagent); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents:  BIOL (Biological
       study)
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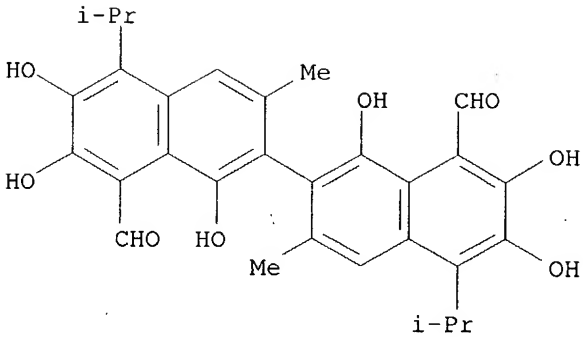

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

111 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
112 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> b home
FILE 'HOME' ENTERED AT 13:27:06 ON 24 NOV 2004

=>

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=> b hcaplus
FILE 'HCAPLUS' ENTERED AT 13:25:48 ON 24 NOV 2004
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FILE COVERS 1907 - 24 Nov 2004  VOL 141 ISS 22
FILE LAST UPDATED: 23 Nov 2004  (20041123/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d que l30
L27 (        19)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("FLACK M"/AU OR "FLACK M
                R"/AU) OR ("FLACK MARY"/AU OR "FLACK MARY R"/AU)
L28 (        45)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("KNAZEK R"/AU OR "KNAZEK R
                A"/AU OR "KNAZEK RICHARD"/AU OR "KNAZEK RICHARD A"/AU OR
                "KNAZEK RICHARD ALLAN"/AU)
L29 (       144)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("REIDENBERG M"/AU OR
                "REIDENBERG M M"/AU OR "REIDENBERG MARCUS"/AU OR "REIDENBERG
                MARCUS M"/AU) OR "REIDENBERN MARCUS M"/AU
L30           1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L27 AND L28 AND L29


=> d all l30

L30  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
AN   1991:485409  HCAPLUS
DN   115:85409
ED   Entered STN:  06 Sep 1991
TI   Gossypol and related compounds for the treatment of cancer
IN   Flack, Mary R.; Knazek, Richard; Reidenberg,
     Marcus
PA   National Institutes of Health, USA
SO   U. S. Pat. Appl., 20 pp. Avail. NTIS Order No. PAT-APPL-7-551 353.
     CODEN: XAXXAV
DT   Patent
LA   English
CC   1-6 (Pharmacology)
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.          DATE
     --------------      ----   --------    --------------------     --------
PI   US 551353           A0     19910415    US 1990-551353           19900712
     US 5385936          A      19950131
     US 6114397          A      20000905    US 1995-379872           19950127
```

PRAI US 1990-551353 A3 19900712
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 551353		

AB Gossypol (I) and related compds. are provided as antitumor agents effective against human cancers. In a study of the effect of I on SW-13 tumor-bearing nude mice, tumor prevalence had dropped from 71 to 54% after 12 wk in the treatment group, while tumor prevalence had risen in the control group; there was no significant effect on body wts. During the study period, 8.3 and 41.6%, resp., of I-treated and control animals died. Preliminary results of I treatment in a clin. trial with metastatic adrenocortical carcinoma patients are also given.

ST gossypol neoplasm inhibitor; metastatic adrenocortical carcinoma inhibitor gossypol

IT Neoplasm inhibitors
(gossypol)

IT Adrenal cortex, neoplasm
(carcinoma, treatment of, with gossypol)

IT Neoplasm inhibitors
(carcinoma, metastasis, adrenocortical, gossypol)

IT 303-45-7, Gossypol
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm inhibitor)

=> => b home
FILE 'HOME' ENTERED AT 13:26:30 ON 24 NOV 2004

=>

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=> b hcaplus
FILE 'HCAPLUS' ENTERED AT 13:23:59 ON 24 NOV 2004
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FILE COVERS 1907 - 24 Nov 2004  VOL 141 ISS 22
FILE LAST UPDATED: 23 Nov 2004  (20041123/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

'OBI' IS DEFAULT SEARCH FIELD FOR 'HCAPLUS' FILE

=> d que l18
L12 (         1)SEA FILE=REGISTRY ABB=ON  PLU=ON  "(-)-GOSSYPOL"/CN
L13 (       112)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12
L14 (    323433)SEA FILE=HCAPLUS ABB=ON  PLU=ON  NEOPLASM?/CT,CW
L15 (    188471)SEA FILE=HCAPLUS ABB=ON  PLU=ON  "ANTITUMOR AGENTS"+OLD,NT/CT
L16 (    478254)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?CANCER?/BI OR L14 OR L15
L17 (        20)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L13 AND L16
L18             6 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 AND (PRY<=1990 OR
                  PY<=1990 OR AY<=1990)


=> b medl
FILE 'MEDLINE' ENTERED AT 13:24:08 ON 24 NOV 2004

 FILE LAST UPDATED: 23 NOV 2004 (20041123/UP).  FILE COVERS 1950 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded.  See HELP RLOAD
 for details.

 OLDMEDLINE now back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d que l25
L19 (       744)SEA FILE=MEDLINE ABB=ON  PLU=ON  GOSSYPOL/CT(L)(PD OR TU OR PK
                  OR AD)
L20 (    610746)SEA FILE=MEDLINE ABB=ON  PLU=ON  "ANTINEOPLASTIC AGENTS"+NT/CT
```

Mitochondria: EN, enzymology
Oncogenes
Protein Kinase C: ME, metabolism
RNA, Messenger: DE, drug effects
Stereoisomerism
Tumor Cells, Cultured
beta 2-Microglobulin: BI, biosynthesis
beta 2-Microglobulin: GE, genetics
RN 303-45-7 (Gossypol)
CN 0 (Antineoplastic Agents); 0 (Calmodulin); 0 (Heat-Shock Proteins); 0 (Isoenzymes); 0 (RNA, Messenger); 0 (beta 2-Microglobulin); EC 2.5.1.18 (Glutathione Transferase); EC 2.7.1.37 (Protein Kinase C)

L26 ANSWER 2 OF 19 MEDLINE on STN
ACCESSION NUMBER: 89288013 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2736516
TITLE: An in vitro and in vivo study of antitumor effects of gossypol on human SW-13 adrenocortical carcinoma.
AUTHOR: Wu Y W; Chik C L; Knazek R A
CORPORATE SOURCE: Developmental Endocrinology Branch, National Institute of Child Health and Development, Bethesda, Maryland 20892.
SOURCE: Cancer research, **(1989 Jul 15)** 49 (14) 3754-8.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198908
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19890803

AB The present study investigated the in vitro and in vivo antitumor effects of gossypol on human SW-13 adrenocortical carcinoma cells. In vitro gossypol concentrations greater than or equal to 0.5 microM reduced the growth rate of the SW-13 cells. Membrane microviscosity was determined by fluorescence polarization of diphenylhexatriene. The membranes of viable SW-13 cells exposed to gossypol became more rigid after a 1-day exposure to gossypol, the polarization constant, P, increasing from 0.229 to 0.352. Gossypol also increased the microviscosities of isolated mitochondrial and microsomal enriched membrane preparations. Tumor was also transplanted into nude mice by s.c. injection of SW-13 cells. A 1-week pretreatment period followed by daily administration of gossypol in which 30 mg gossypol/kg body weight/day was administered via orogastric tube delayed the onset of visible tumor in the subsequent weeks. Five weeks after transplantation, tumor prevalence rate was 95.8% in the control group and 54.5% in the gossypol-treated group. A second experiment, consisting of 12 weeks of gossypol treatment, reduced a preexisting 71% tumor prevalence to 54% while the tumor prevalence increased to 83% in the control group. This was accompanied by a 41.6% mortality in the control group versus 8.3% in the gossypol-treated group. These data suggest that gossypol may provide a beneficial effect in patients with adrenocortical carcinoma.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't
*Adrenal Cortex Neoplasms: DT, drug therapy
Adrenal Cortex Neoplasms: PA, pathology
Animals
***Antineoplastic Agents**
Cell Division: DE, drug effects
Cell Line

Cell Membrane: DE, drug effects
Cell Membrane: UL, ultrastructure
Gossypol: PD, pharmacology
***Gossypol: TU, therapeutic use**
Mice
Mice, Nude
Microsomes: DE, drug effects
Microsomes: UL, ultrastructure
Mitochondria: DE, drug effects
Mitochondria: UL, ultrastructure
Neoplasm Transplantation
Transplantation, Heterologous
*Tumor Cells, Cultured: CY, cytology
Tumor Cells, Cultured: DE, drug effects
Viscosity
RN 303-45-7 (Gossypol)
CN 0 (Antineoplastic Agents)

L26 ANSWER 3 OF 19 MEDLINE on STN
ACCESSION NUMBER: 89195127 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2539251
TITLE: Modulation of 4'-(9-acridinylamino)methanesulfon-m-anisidide-induced, topoisomerase II-mediated DNA cleavage by gossypol.
COMMENT: Erratum in: Cancer Res 1989 Jun 1;49(11):3142
AUTHOR: Adlakha R C; Ashorn C L; Chan D; Zwelling L A
CORPORATE SOURCE: Department of Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston 77030.
CONTRACT NUMBER: CA-40090 (NCI)
RR5511-23 (NCRR)
SOURCE: Cancer research, **(1989 Apr 15)** 49 (8) 2052-8.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198905
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19970203
Entered Medline: 19890524

AB Our earlier studies have shown that gossypol [1,1',6,6',7,7'-hexahydroxy-5,5-diisopropyl - 3,3'-dimethyl - (2,2'- binaphthalene)-8,8'-dicarboxyaldehyde], a male contraceptive, inhibits DNA synthesis by decreasing the activities of DNA polymerase alpha and beta, resulting in the arrest of cells in mid-S phase [L.J. Rosenberg, R.C. Adlakha, D.M. Desai, and P.N. Rao, Biochim. Biophys. Acta, 866: 258-267, 1986]. Now we have examined the effects of gossypol on another enzyme of importance to cellular functions, topoisomerase II (topo II). We have determined the consequences of gossypol treatment on 4'-(9-acridinylamino)methane-sulfon-m anisidide (m-AMSA)-induced topoisomerase II-mediated, protein-associated DNA cleavage using the alkaline elution technique. In HeLa cells pretreated with gossypol (3.4-17.5 microM) for 8-16 h we observed a dose- and time-dependent decrease (50-75%) in DNA cleavage compared to that quantified in cells treated with m-AMSA alone. Gossypol by itself did not induce more than 25 rad-equivalents of DNA single-strand breaks even at the highest dose tested (26 microM). [14C]m-AMSA uptake was identical in treated and untreated cells. Pretreatment of cells with another inhibitor of DNA synthesis, thymidine, which blocks cells at G1/S boundary increased

the m-AMSA-induced DNA cleavage by 25%, suggesting that the effect of gossypol might be due to the arrest of cells in mid-S phase. In contrast to gossypol's effects on m-AMSA-induced DNA cleavage, m-AMSA-induced cytotoxicity was actually increased in gossypol pretreated cells. Gossypol blocked topo II strand passing activity (decatenation of kinetoplast DNA) of cellular extracts from HeLa cells. The inhibition of this activity by gossypol was synergistic with the inhibition produced by m-AMSA or etoposide. These data suggest that gossypol can both inhibit topo II catalytic activity and interfere with the stabilization of topo II-DNA complex formation by m-AMSA. These data indicate that the magnitude of m-AMSA-induced DNA cleavage may not necessarily parallel the magnitude of m-AMSA-induced cytotoxicity. The cytotoxicity data may rather be explained by an action of gossypol and m-AMSA to block topo II catalytic activity at a point in the enzyme's strand passing cycle prior to cleavage complex formation that might be particularly toxic to cells in S phase. Gossypol should therefore be useful in improving our understanding of the cellular role of topo II and the consequences of interference with topo II activity by active antineoplastic agents.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Amsacrine: PK, pharmacokinetics
***Amsacrine: PD, pharmacology**
*DNA: DE, drug effects
*DNA Damage
*DNA Topoisomerases, Type I: PH, physiology
***Gossypol: PD, pharmacology**
Hela Cells

RN 303-45-7 (Gossypol); 51264-14-3 (Amsacrine); 9007-49-2 (DNA)
CN EC 5.99.1.2 (DNA Topoisomerases, Type I)

L26 ANSWER 4 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 89280405 EMBASE
DOCUMENT NUMBER: 1989280405
TITLE: The effect of gossypol and 6-aminonicotinamide on tumor cell metabolism: A 31P-magnetic resonance spectroscopic study.
AUTHOR: Keniry M.A.; Hollander C.; Benz C.C.
CORPORATE SOURCE: Research School of Chemistry, Australian National University, Canberra, ACT 2601, Australia
SOURCE: Biochemical and Biophysical Research Communications, (1989) 164/2 (947-953).
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB 31P-Magnetic resonance spectroscopy has been used to assess the changes in the levels of water-soluble phosphate pools in T47-D breast carcinoma cells induced by the antimitochondrial drugs, gossypol and 6-aminonicotinamide. A decrease in the NTP/Pi ratio occurred after treatment with gossypol. No change in the NTP/Pi ratio occurred on treatment with 6-aminonicotinamide; however, a substantial accumulation of 6-phosphogluconate was observed. Pretreatment of T47-D cells with gossypol prevented the accumulation of 6-phosphogluconate. This facile and non-invasive approach suggests that the oxidative part of the

(Uses)
(neoplasm inhibiting activity of, in gonadal **cancer**, cell proliferation inhibition in relation to)

L26 ANSWER 6 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1988:504364 HCAPLUS
DOCUMENT NUMBER: 109:104364
TITLE: Gossypol, a cytotoxic agent, may uncouple respiration of Ehrlich ascites tumor cells
AUTHOR(S): McSheehy, P. M. J.; Bashford, C. L.
CORPORATE SOURCE: Med. Sch., St. George's Hosp., London, SW17 0RE, UK
SOURCE: Biochemical Society Transactions (**1988**), 16(4), 616-17
CODEN: BCSTB5; ISSN: 0300-5127
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cytotoxic mechanism (I), as a potential antitumor agent, was studied by evaluating the kinetics of I (9-94 μM) action on the metabolism of Ehrlich ascites tumor cells (Lettre cells) by measuring the phosphorylation potential and O consumption. The results of the study are not consistent with gossypol acting as a glycolytic inhibitor, but rather as having an uncoupler-like effect on the cell leading to subsequent cell lysis and death. The predominantly glycolytic nature of tumor cells, even under conditions of high O tension, would be likely to make tumors less sensitive than host tissue to gossypol cytotoxicity. Thus these results do not correlate with the proposal that gossypol has a role in chemotherapy.
CC 1-6 (Pharmacology)
IT **Neoplasm inhibitors**
(gossypol in relation to)
IT **90141-22-3**, (-)-Gossypol
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(glycolytic inhibitory and respiratory uncoupling effects of, on Ehrlich ascites tumor cells)

L26 ANSWER 7 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 88091803 EMBASE
DOCUMENT NUMBER: 1988091803
TITLE: Selective toxicity of gossypol against epithelial tumors and its detection by magnetic resonance spectroscopy.
AUTHOR: Benz C.; Keniry M.; Goldberg H.
CORPORATE SOURCE: Cancer Research Institute, University of California, San Francisco, CA, United States
SOURCE: Contraception, (1988) 37/3 (221-228).
ISSN: 0010-7824 CODEN: CCPTAY
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 010 Obstetrics and Gynecology
016 Cancer
028 Urology and Nephrology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The antitumor toxicity of gossypol was measured in 6 human carcinoma cell lines and compared with its toxicity against human bone marrow stem cells. Marrow cells were more resistant than any of the tumor cell lines, and

tumor cell sensitivity depended on the content of intracellular LDH-M. [31P]-Magnetic resonance spectroscopy showed decline in tumor ATP levels occurring within 24 hours of treatment, suggesting that this non-invasive technique may serve as an early biochemical monitor of gossypol toxicity.

CT Medical Descriptors:
*cell line
***epithelium tumor**
cell culture
nuclear magnetic resonance
priority journal
human cell
human
male
female
Drug Descriptors:
***antineoplastic agent**
***gossypol: PD, pharmacology**

RN (gossypol) 303-45-7

L26 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:51382 HCAPLUS
DOCUMENT NUMBER: 110:51382
TITLE: Determination of gossypol enantiomers in plasma after administration of racemate using high-performance liquid chromatography with precolumn chemical derivatization
AUTHOR(S): Wu, Da Fang; Reidenberg, Marcus M.; Drayer, Dennis E.
CORPORATE SOURCE: Med. Coll., Cornell Univ., New York, NY, 10021, USA
SOURCE: Journal of Chromatography (**1988**), 433, 141-8
CODEN: JOCRAM; ISSN: 0021-9673
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A HPLC assay with precolumn chemical derivatization was developed for the determination of gossypol enantiomers in plasma, after administration of the racemate. Racemic gossypol acetic acid in plasma was extracted into acetonitrile and analyzed using a reversed-phase column and a coulometric detector in the redox mode. To sep. the enantiomers, 30 μL of the chiral derivatizing reagent, (R)-(-)-2-amino-1-propanol (50 mg/mL) and 15 μL of 20% (volume/vol) acetic acid were added to the acetonitrile layer which was then heated at 60° for 100 min. The mobile phase used to resolve the derivatized enantiomers was 0.2M phosphate buffer (pH 3.5)-acetonitrile (38:62, volume/volume). At a flow rate of 1.5 mL/min, the retention times for derivatized (+)-gossypol and (-)-gossypol were 4.0 and 7.8 min, resp. Two **cancer** patients received 10 mg racemic gossypol acetic acid 3 times a day. In 1 patient, the racemic, (+)- and (-)-gossypol acetic acid plasma concns. after 65 days of therapy were 317, 213, and 104 ng/mL, resp. In the other patient, these values were 362, 210, and 152 ng/mL, resp., after a week of therapy.

CC 2-1 (Mammalian Hormones)

IT 20300-26-9, (+)-Gossypol **90141-22-3**, (-)-Gossypol
RL: ANT (Analyte); ANST (Analytical study)
(determination of, in blood plasma of human by HPLC with precolumn derivatization)

L26 ANSWER 9 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 87077188 EMBASE
DOCUMENT NUMBER: 1987077188

TITLE: Lactic dehydrogenase isozymes, 31P magnetic resonance spectroscopy, and in vitro antimitochondrial tumor toxicity with gossypol and rhodamine-123.
AUTHOR: Benz C.; Hollander C.; Keniry M.; et al.
CORPORATE SOURCE: Cancer Research Institute, University of California, San Francisco, CA 94143, United States
SOURCE: Journal of Clinical Investigation, (1987) 79/2 (517-523). CODEN: JCINAO
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
029 Clinical Biochemistry
016 Cancer
030 Pharmacology
LANGUAGE: English

AB Three compounds that share specific antimitochondrial properties are gossypol, rhodamine-123, and lonidamine. We compare the antiproliferative activities of these drugs against six human cell lines derived from breast (T47-D), pancreas (MiaPaCa, RWP-2), prostate (DU-145), colon (HCT-8), and cervix (HeLa) carcinomas. Tumor cells enriched in cathodal LDH isozymes (LDH4 and LDH5) are significantly more sensitive to gossypol and rhodamine-123. When compared for ability to inhibit growth of human marrow in soft agar, 10 μM gossypol shows little effect on colony formation whereas 10 μM rhodamine-123 completely prevents stem cell growth, suggesting that gossypol may have the most favorable therapeutic index. Within 24 h of drug administration, there is a relative increase in intracellular inorganic phosphate pools and a marked decline in soluble high-energy phosphates in sensitive tumor cells, as measured by 31P magnetic resonance spectroscopy. These studies suggest that specific antimitochondrial agents might be selectively administered on the basis of tumor LDH isozyme content and noninvasively monitored for antiproliferative activity by 31P spectroscopy.

CT Medical Descriptors:
***breast cancer**
*cell growth
***colon cancer**
*drug comparison
*drug cytotoxicity
*drug efficacy
*drug interaction
*drug mechanism
*nuclear magnetic resonance
***pancreas cancer**
***prostate cancer**
***uterine cervix cancer**
breast carcinoma
colon carcinoma
human cell
pancreas carcinoma
prostate carcinoma
uterine cervix carcinoma
priority journal
intoxication
pancreas
male genital system
large intestine
female genital system
drug administration

preliminary communication
in vitro study
human
endocrine system
breast
Drug Descriptors:
***gossypol**
*lactate dehydrogenase isoenzyme
***lonidamine**
*rhodamine 123
radioisotope
RN (gossypol) 303-45-7; (lonidamine) 50264-69-2; (rhodamine 123) 62669-70-9
CO Sigma; Angelini (Italy)

L26 ANSWER 10 OF 19 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 87324751 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3631888
TITLE: Influence of 5-hydroxytryptamine on the combination effect of lonidamine or gossypol and hyperthermia on Ehrlich tumour in vivo.
AUTHOR: Molla M R; Yoshiga K; Takada K
SOURCE: Anticancer research, **(1987 May-Jun)** 7 (3 Pt B) 361-4.
Journal code: 8102988. ISSN: 0250-7005.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198709
ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19870929
AB An experiment was conducted using lonidamine and gossypol against Ehrlich tumour in the foot pad of CD-1 mice. These compounds alone were mild antitumour agents, but their cytotoxicity increased when they were combined with hyperthermia. The antitumor effect was further increased by 5-hydroxytryptamine, particularly when combined with lonidamine.
CT Check Tags: Male; Support, Non-U.S. Gov't
Animals
***Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use**
*Carcinoma, Ehrlich Tumor: TH, therapy
Combined Modality Therapy
***Gossypol: AD, administration & dosage**
Hydrogen-Ion Concentration
*Hyperthermia, Induced
*Indazoles: AD, administration & dosage
Mice
*Pyrazoles: AD, administration & dosage
*Serotonin: PD, pharmacology
RN 303-45-7 (Gossypol); 50-67-9 (Serotonin); 50264-69-2 (lonidamine)
CN 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Indazoles); 0 (Pyrazoles)

L26 ANSWER 11 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1986:583551 HCAPLUS
DOCUMENT NUMBER: 105:183551
TITLE: Cytotoxicity of enantiomers of gossypol

generation of active oxygen species via redox cycling. Certain quinones have been shown to be mutagenic via the formation of active oxygen species and others via their conversion to DNA-binding semiquinone free radicals. Paradoxically, quinones are not only mutagenic and therefore potentially carcinogenic, they are also effective anticancer agents. Classic examples are Adriamycin (doxorubicin hydrochloride) and mitomycin C, but other less complex quinones also show effective antitumor activity. The design of novel quinones that are more selective in their toxicity to human tumor cells and whose mechanism of action is understood seems a promising approach in cancer treatment, especially if host toxicity can be prevented via the use of chemoprotective agents.

CT Medical Descriptors:
*2,3 dimethylbenzoquinone
*cancer combination chemotherapy
***chemical carcinogenesis**
*drug toxicity
priority journal
therapy
intoxication
drug administration
short survey
methodology
human
nonhuman
animal
ecology
clinical article
animal cell
Drug Descriptors:
*1 naphthol
***antineoplastic agent**
*benzene
*benzoquinone
*carcinogen
***carmustine**
*catechol
***daunorubicin**
***diethylstilbestrol**
***doxorubicin**
*drug metabolite
***gossypol**
***lapachol**
*lawsone
*menadione
***mitomycin c**
*mutagenic agent
***nogalamycin**
*paracetamol
*phenol
*phytomenadione
***zorubicin**
***rufocromomycin**
mitomycin

RN (1 naphthol) 90-15-3; (benzene) 71-43-2; (carmustine) 154-93-8; (catechol) 120-80-9; (daunorubicin) 12707-28-7, 20830-81-3, 23541-50-6; (diethylstilbestrol) 30498-85-2, 56-53-1; (doxorubicin) 23214-92-8, 25316-40-9; (gossypol) 303-45-7; (lapachol) 84-79-7; (lawsone) 83-72-7; (menadione) 58-27-5; (mitomycin c) 50-07-7, 74349-48-7; (nogalamycin)

*diaphragm
*gallbladder disease
*gastrointestinal toxicity
*headache
*hypertension
*intrauterine contraceptive device
*loestrin 1 20
*phenoxybenzaline
*pregnancy
*progesterone containing intrauterine contraceptive device
*uterine cervix dysplasia
priority journal
female genital system
breast
cardiovascular system
gallbladder
intoxication
oral drug administration
short survey
human
prevention
Drug Descriptors:
***conjugated estrogen**
*estrogen
***ethinylestradiol**
*etynodiol
*etynodiol diacetate
*gestagen
*gonadorelin
***gossypol**
*ethinylestradiol plus levonorgestrel
***medroxyprogesterone acetate**
*mestranol
*norethisterone
*norethisterone acetate
*mestranol plus norethisterone
*norgestrel
*ethinylestradiol plus norgestrel
*ethinylestradiol plus norethisterone
*oral contraceptive agent
ampicillin
barbituric acid derivative
carbamazepine
chloramphenicol
ethosuximide
penicillin g
phenytoin
primidone
rifampicin
loestrin 1 20
ethinylestradiol plus etynodiol diacetate
progesterone
unclassified drug
RN (ethinylestradiol) 57-63-6; (etynodiol) 1231-93-2; (etynodiol diacetate) 297-76-7; (gonadorelin) 33515-09-2, 9034-40-6; (gossypol) 303-45-7; (ethinylestradiol plus levonorgestrel) 39366-37-5; (medroxyprogesterone acetate) 71-58-9; (mestranol) 72-33-3; (norethisterone) 68-22-4; (norethisterone acetate) 51-98-9; (mestranol plus norethisterone)

8015-29-0; (norgestrel) 6533-00-2; (ethinylestradiol plus norgestrel) 8056-51-7; (ethinylestradiol plus norethisterone) 37270-71-6; (ampicillin) 69-52-3, 69-53-4, 7177-48-2, 74083-13-9, 94586-58-0; (carbamazepine) 298-46-4, 8047-84-5; (chloramphenicol) 134-90-7, 2787-09-9, 56-75-7; (ethosuximide) 77-67-8; (penicillin g) 1406-05-9, 61-33-6; (phenytoin) 57-41-0, 630-93-3; (primidone) 125-33-7; (rifampicin) 13292-46-1; (ethinylestradiol plus etynodiol diacetate) 8075-78-3; (progesterone) 57-83-0

CN Loestrin 1 20; Norinyl; Ortho novum 777; Depo provera; Nordette; Trinorinyl; Ovrette; Demulen; Progestasert; Premarin; Triphasil; Brevicon; Ovral; Modicon

L26 ANSWER 15 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 85155611 EMBASE
DOCUMENT NUMBER: 1985155611
TITLE: Antitumor effects of gossypol on murine tumors.
AUTHOR: Rao P.N.; Yong-Chao Wang; Lotzova E.; et al.
CORPORATE SOURCE: Department of Chemotherapy Research, The University of Texas M.D. Anderson Hospital and Tumor Institute at Houston, Houston, TX 77030, United States
SOURCE: Cancer Chemotherapy and Pharmacology, (1985) 15/1 (20-25). CODEN: CCPHDZ
COUNTRY: Germany
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
030 Pharmacology
016 Cancer
052 Toxicology
LANGUAGE: English

AB Since the male antifertility drug, gossypol, was shown to be a specific inhibitor of DNA synthesis at moderately low doses in cultured cells, its antitumor potential has been evaluated in three murine tumor models. The effects of gossypol on tumor growth and the survival of 10- to 12-week-old BDF1 mice bearing mouse mammary adenocarcinoma 755 (Ca 755) or P388 or L1210 leukemias, all injected IP, were measured. At an optimum dose of 0.5 mg/mouse given as a single injection at 2 days (48 h) after the inoculation of 105 Ca 755 tumor cells, gossypol rendered 66% of the mice free of tumor cells, whereas the remaining 34% died of drug toxicity. The survival rate decreased sharply at doses on either side of the optimum. At suboptimal doses a major proportion of the tumor-bearing mice died of tumor, whereas at higher doses all the animals died of drug toxicity. In other words, the effective dose range of gossypol was rather narrow. The rapidly proliferating mouse leukemias, P388 and L1210, failed to respond to gossypol. Histopathological studies of various organs in the gossypol-treated mice revealed no consistent lesions that could give an indication of organ-specific toxicity of gossypol. The reduction in the myeloid series in the bone marrow of gossypol-treated mice may have been due to depletion rather than direct toxic effect. Further studies are essential to evaluate this compound with regard to its antitumor activity in other murine models.

CT Medical Descriptors:
***breast cancer**
*cancer cell culture
*cancer chemotherapy
***cancer growth**
*drug efficacy
*drug toxicity

***leukemia**
histopathology
mouse
priority journal
therapy
intoxication
intraperitoneal drug administration
methodology
nonhuman
animal experiment
animal model
Drug Descriptors:
***antineoplastic agent**
***gossypol**
RN (gossypol) 303-45-7
CO Southwest research foundation (United States)

L26 ANSWER 16 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 85021195 EMBASE
DOCUMENT NUMBER: 1985021195
TITLE: [Genital virus infections. Their treatment].
LES VIROSES GENITALES. A PROPOS DE LEUR TRAITEMENT.
AUTHOR: Legros R.; Coupez F.; Louis E.
CORPORATE SOURCE: Service de Gynecologie Chirurgicale et de Senologie, Centre Hospitalier, F 94010 Creteil Cedex, France
SOURCE: Gynecologie, (1984) 35/4 (303-311).
CODEN: GYNCAZ
COUNTRY: France
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
010 Obstetrics and Gynecology
047 Virology
013 Dermatology and Venereology
030 Pharmacology
LANGUAGE: French
SUMMARY LANGUAGE: English
AB The treatment of condylomas of the uterine cervix occupies a justified place amongst current preoccupations in gynaecology. The role of the CO2 laser is preponderant but not unique. The authors report on this study their experience based upon 169 of condylomas. However HPV virus infections account for only a proportion of genital virus disorders and the local treatment of condylomas cannot alone cover all therapeutic possibilities. Even if results obtained by medical methods are often disappointing, they must nevertheless be analysed and their limitations assessed. The existence of a virus infection during pregnancy requires special management, above all because of possible consequences for the newborn infant. The selection of populations with a greater oncogenic risk is possible. This is progress of great interest whilst awaiting the day when the vaccination of young patients will become possible.
CT Medical Descriptors:
***condyloma**
*genital tract infection
*genital herpes
*herpes simplex virus 2
*papilloma virus
*drug therapy
laser

pregnancy
therapy
human
Drug Descriptors:
***fiacitabine**
*aciclovir
***azathioprine**
***bleomycin**
*5 (2 bromovinyl) 2' deoxyuridine
*colchicine
***fluorouracil**
***gossypol**
*herpes vaccine
*idoxuridine
*interferon
*methisoprinol
*foscarnet
*podophyllin
*trifluridine
*vidarabine
RN (fiacitabine) 69123-90-6; (aciclovir) 59277-89-3; (azathioprine) 446-86-6; (bleomycin) 11056-06-7; (5 (2 bromovinyl) 2' deoxyuridine) 69304-47-8, 82768-44-3; (colchicine) 64-86-8; (fluorouracil) 51-21-8; (gossypol) 303-45-7; (idoxuridine) 54-42-2; (methisoprinol) 36703-88-5; (foscarnet) 4428-95-9; (podophyllin) 9000-55-9; (trifluridine) 70-00-8; (vidarabine) 2006-02-2, 5536-17-4
CN Imurel; Zovirax; Iduviran

L26 ANSWER 17 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 84102554 EMBASE
DOCUMENT NUMBER: 1984102554
TITLE: The effect of gossypol and lonidamine on electron transport in Ehrlich ascites tumor mitochondria.
AUTHOR: Floridi A.; D'Atri S.; Bellocci M.; et al.
CORPORATE SOURCE: Regina Elena Institute for Cancer Research, 00161 Rome, Italy
SOURCE: Experimental and Molecular Pathology, (1984) 40/2 (246-261).
CODEN: EXMPA6
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
005 General Pathology and Pathological Anatomy
030 Pharmacology
048 Gastroenterology
016 Cancer
LANGUAGE: English
AB The effect of the association of gossypol and Lonidamine on the electron transport in Ehrlich ascites tumor mitochondria has been investigated by addition of drugs to isolated mitochondria. The results may be summarized as follows. (1) Low concentrations of gossypol increase the rate of oxygen consumption at the level of three energy-conserving sites of the respiratory chain. Higher concentrations result in an inhibition of oxygen consumption at (or near) both energy-conserving sites 1 and 2, while energy-conserving site 3 is unaffected. (2) Gossypol, at concentrations at which it exerts its uncoupling effect, stimulates ATPase activity. Higher concentrations inhibit the enzyme activity. (3) The addition of gossypol

to mitochondria respiring on pyruvate plus malate or succinate induces a more oxidized state of NAD+ and cytochrome b, respectively. (4) gossypol enhances the effect of Lonidamine on oxygen consumption. Lonidamine does not affect state 4 respiration, but in the presence of gossypol, it determines a marked decrease in the rate of oxygen consumption. The inhibition of oxidation of NAD-linked substrates is greater than that of FAD-linked substrates. (5) It may be concluded that gossypol is very effective in potentiating the effect of Lonidamine. Moreover, it may be suggested that the antitumor activity of Lonidamine is enhanced if it is used in combination with other drugs and/or treatments, such as hyperthermia, which modify the energy status of mitochondria.

CT Medical Descriptors:
***cancer cell**
***ehrlich ascites tumor**
*electron transport
*mitochondrion
*oxygen consumption
cancer chemotherapy
ehrlich ascites
nonhuman
therapy
Drug Descriptors:
*adenosine triphosphatase
***gossypol**
***lonidamine**
enzyme

RN (adenosine triphosphatase) 37289-25-1, 9000-83-3; (gossypol) 303-45-7; (lonidamine) 50264-69-2

CO Poliscience (United States)

L26 ANSWER 18 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 83232276 EMBASE
DOCUMENT NUMBER: 1983232276
TITLE: Dietary carcinogens and anticarcinogens. Oxygen radicals and degenerative diseases.
AUTHOR: Ames B.N.
CORPORATE SOURCE: Dep. Biochem., Univ. California, Berkeley, CA 94720, United States
SOURCE: Science, (1983) 221/4617 (1256-1263).
CODEN: SCIEAS
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
017 Public Health, Social Medicine and Epidemiology
052 Toxicology
030 Pharmacology
016 Cancer
LANGUAGE: English

AB The human diet contains a great variety of natural mutagens and carcinogens, as well as many natural antimutagens and anticarcinogens. Many of these mutagens and carcinogens may act through the generation of oxygen radicals. Oxygen radicals may also play a major role as endogenous initiators of degenerative processes, such as DNA damage and mutation (and promotion), that may be related to cancer, heart disease, and aging. Dietary intake of natural antioxidants could be an important aspect of the body's defense mechanism against these agents. Many antioxidants are being identified as anticarcinogens. Characterizing and optimizing such defense

systems may be an important part of a strategy of minimizing cancer and other age-related diseases.

CT Medical Descriptors:
*age
***cancer**
*chaconine
***chemical carcinogenesis**
*convicine
*dna damage
*dna synthesis
*diet
*drug toxicity
*heart disease
*malvalic acid
*methyleugenol
*mutation
*sterculic acid
*vicine
aging
heart
intoxication
review
human
etiology
Drug Descriptors:
*allyl isothiocyanate
*alpha tocopherol
*anagyrine
***antineoplastic agent**
*ascorbic acid
*beta carotene
*canavanine
*carcinogen
*estragole
*alcohol
*glutathione
***gossypol**
*lactone derivative
*mutagenic agent
*oxygen radical
*phorbol ester
*psoralen derivative
*pyrrolizidine derivative
*quercetin
*quinone derivative
*safrole
*selenium
*solanine
*theobromine
*uric acid
antimutagenic agent
antioxidant

RN (allyl isothiocyanate) 57-06-7; (alpha tocopherol) 1406-18-4, 1406-70-8, 52225-20-4, 58-95-7, 59-02-9; (anagyrine) 486-89-5; (ascorbic acid) 134-03-2, 15421-15-5, 50-81-7; (beta carotene) 7235-40-7; (canavanine) 543-38-4; (estragole) 140-67-0; (alcohol) 64-17-5; (glutathione) 70-18-8; (gossypol) 303-45-7; (quercetin) 117-39-5; (safrole) 94-59-7; (selenium) 7782-49-2; (solanine) 20562-02-1, 51938-42-2; (theobromine) 83-67-0; (uric

acid) 69-93-2

L26 ANSWER 19 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 83198979 EMBASE
DOCUMENT NUMBER: 1983198979
TITLE: The effect of the association of gossypol and lonidamine on the energy metabolism of Ehrlich ascites tumor cells.
AUTHOR: Floridi A.; D'Atri S.; Menichini R.; et al.
CORPORATE SOURCE: Reginal Elena Inst. Cancer Res., 00161 Rome, Italy
SOURCE: Experimental and Molecular Pathology, (1983) 38/3 (322-335).
CODEN: EXMPA6
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
005 General Pathology and Pathological Anatomy
029 Clinical Biochemistry
048 Gastroenterology
016 Cancer
030 Pharmacology
LANGUAGE: English
AB The effect of the association of Gossypol and Lonidamine on the energy metabolism of Ehrlich ascites tumor cells has been investigated. The action of the drug on tumor cells was studied by addition of the drugs to cells harvested from Swiss male mice. The results may be summarized as follows: (1) Low concentrations of gossypol increase the rate of oxygen consumption by uncoupling oxidative phosphorylation. High concentrations result in an inhibition of oxygen consumption with a mechanism that must be regarded as not directly related to the uncoupling activity. (2) Gossypol, at concentrations at which it exerts an uncoupling activity, stimulates mitochondrial ATPase which in turn increases the aerobic and anaerobic rates of lactate production. The decrease of glycolysis at high concentrations of Gossypol does not depend on the inhibition of enzymes of the glycolytic pathway, but must be ascribed to cell death. (3) The association of a low concentration of Gossypol with Lonidamine brings about a further inhibition of oxygen consumption. Moreover, Lonidamine abolishes the stimulation of glycolysis induced by Gossypol and lowers lactate production to values that are quite similar to those found with Lonidamine alone. (4) It may be concluded that the association of Gossypol and Lonidamine results in a very effective decrease of the energy requirements of cancer cells.
CT Medical Descriptors:
*ascites
***cancer cell**
*drug efficacy
***ehrlich ascites tumor cell**
*energy transfer
***tumor cell**
mouse
oxygen consumption
nonhuman
blood and hemopoietic system
in vitro study
Drug Descriptors:
***gossypol**
***lonidamine**
*oligomycin

*ouabain
lactic acid
proton transporting adenosine triphosphate synthase
RN (gossypol) 303-45-7; (lonidamine) 50264-69-2; (oligomycin) 1404-19-9; (ouabain) 11018-89-6, 630-60-4; (lactic acid) 113-21-3, 50-21-5; (proton transporting adenosine triphosphate synthase) 37205-63-3

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- *I am an examiner in Workgroup:* ☐ *Example: 1610*
- *Relevant prior art **found**, search results used as follows:*
  - ☐ 102 rejection
  - ☐ 103 rejection
  - ☐ Cited as being of interest.
  - ☐ Helped examiner better understand the invention.
  - ☐ Helped examiner better understand the state of the art in their technology.

Types of relevant prior art found:

- ☐ Foreign Patent(s)
- ☐ Non-Patent Literature
  (journal articles, conference proceedings, new product announcements etc.)

- *Relevant prior art **not found:***
  - ☐ Results verified the lack of relevant prior art (helped determine patentability).
  - ☐ Results were not useful in determining patentability or understanding the invention.

Comments:

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1404-15-5; (paracetamol) 103-90-2; (phenol) 108-95-2, 3229-70-7; (phytomenadione) 11104-38-4, 84-80-0; (zorubicin) 36508-71-1, 54083-22-6; (rufocromomycin) 11031-41-7, 3930-19-6; (mitomycin) 1404-00-8

L26 ANSWER 13 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1986:199755 HCAPLUS
DOCUMENT NUMBER: 104:199755
TITLE: Comparison of action of racemic (±) and optically active (- and +) gossypols on HeLa cells
AUTHOR(S): Zhang, Jingbo; Zhang, Shifu; Yuan, Ju; Xu, Kaiming
CORPORATE SOURCE: Inst. Basic Med. Sci., Chin. Acad. Med. Sci., Beijing, Peop. Rep. China
SOURCE: Zhongguo Yixue Kexueyuan Xuebao (**1985**), 7(5), 384-7
CODEN: CIHPDR; ISSN: 0253-3774
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB In HeLa cell cultures, (-)-gossypol [**90141-22-3**] and (±)-gossypol [40112-23-0] inhibited the cell growth, DNA synthesis, and cell division, whereas (+)-gossypol [20300-26-9] had no effect. The effective concentration of the (-)-isomer is 2-fold less than that of racemic gossypol, suggesting that the antitumor activity of racemic gossypol is due to the (-)-isomer.
CC 1-6 (Pharmacology)
IT **Neoplasm inhibitors**
(gossypol isomers as)
IT 303-45-7 20300-26-9 **90141-22-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(neoplasm-inhibiting activity of)

L26 ANSWER 14 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 86030718 EMBASE
DOCUMENT NUMBER: 1986030718
TITLE: Prescription contraceptives: Countering the risks.
AUTHOR: Ruggiero R.J.
CORPORATE SOURCE: Division of Clinical Pharmacy, Department of Pharmaceutical Services, University of California, Los Angeles, CA, United States
SOURCE: American Pharmacy, (1985) 25/9 (32-37).
CODEN: AMPHDF
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 038 Adverse Reactions Titles
037 Drug Literature Index
LANGUAGE: English
CT Medical Descriptors:
*adverse drug reaction
*breakthrough bleeding
***breast cancer**
*breast feeding
*mastalgia
***carcinogenesis**
*candidiasis
*cardiovascular disease
*contraception

AUTHOR(S): Joseph, A. E. A.; Matlin, S. A.; Knox, P.
CORPORATE SOURCE: Dep. Radiol., St. George's Hosp., London, SW17 0QT, UK
SOURCE: British Journal of Cancer (**1986**), 54(3), 511-13
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Racemic gossypol [40112-23-0] inhibited proliferation of both normal fibroblasts and tumor-derived cells. (-)-Gossypol **[90141-22-3]** was much more cytotoxic than was (+)-gossypol [20300-26-9], a difference similar to that reported for production of infertility. A (-)-gossypol concentration of 1.9 μg/mL caused a 50% reduction in cell growth of human fibroblasts, and 50% cell lysis was attained with .apprx.10 μg gossypol/mL. Although cell lysis did not become visible for .apprx.16 h, a 30-min exposure time was adequate to induce the cytolytic effect. The cytotoxicity of gossypol was diminished as a result of binding by plasma proteins, which may account for the low incidence of side effects in clin. antifertility studies.

CC 1-6 (Pharmacology)
Section cross-reference(s): 2

IT **Neoplasm inhibitors**
(gossypol and gossypol enantiomers as)

IT 303-45-7 20300-26-9 **90141-22-3**
RL: PRP (Properties)
(cytotoxicity of, in fibroblast and tumor-derived cells)

L26 ANSWER 12 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 86104334 EMBASE
DOCUMENT NUMBER: 1986104334
TITLE: Quinones as mutagens, carcinogens, and anticancer agents: Introduction and overview.
AUTHOR: Smith M.T.
CORPORATE SOURCE: Department of Biomedical and Environmental Health Sciences, School of Public Health, University of California, Berkeley, CA 94720, United States
SOURCE: Journal of Toxicology and Environmental Health, (1985) 16/5 (665-672).
CODEN: JTEHD6
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
052 Toxicology
016 Cancer
030 Pharmacology
017 Public Health, Social Medicine and Epidemiology
025 Hematology
035 Occupational Health and Industrial Medicine
006 Internal Medicine
LANGUAGE: English

AB Quinones are widespread in our environment, occurring both naturally and as pollutants. Human exposure to them is therefore extensive. Quinones also form an important class of toxic metabolites generated as a result of the metabolism of phenols and related compounds, including phenol itself, 1-naphthol, and diethylstilbesterol. The mechanisms by which quinones exert their toxic effect are complex, but two processes appear to be centrally involved: the direct arylation of sulfhydryls, and the

pentose-phosphate shuttle is an important source of reducing equivalents in T47-D cells. This pathway may prove to be a useful target for site-directed drug attack in carcinoma cell lines that require large quantities of NADP for the synthesis of fatty acids and steroids.

CT Medical Descriptors:
*cell metabolism
***tumor cell**
nuclear magnetic resonance
priority journal
Drug Descriptors:
***6 aminonicotinamide: PD, pharmacology**
***gossypol: PD, pharmacology**

RN (6 aminonicotinamide) 329-89-5; (gossypol) 303-45-7

CO Sigma

L26 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1989:165719 HCAPLUS
DOCUMENT NUMBER: 110:165719
TITLE: Antiproliferative effect of gossypol and its optical isomers on human reproductive **cancer** cell lines
AUTHOR(S): Band, Vimla; Hoffer, Anita P.; Bands, Hamid; Rhinehardt, Ann E.; Knapp, Robert C.; Matlin, Stephen A.; Anderson, Deborah J.
CORPORATE SOURCE: Dana Farber Cancer Inst., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Gynecologic Oncology (**1989**), 32(3), 273-7
CODEN: GYNOA3; ISSN: 0090-8258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The antiproliferative effect of gossypol and its optical isomers on various human cell lines of reproductive and nonreproductive tissue origin was studied. Various reproductive **cancer** cell lines of ovarian, gestational, and testicular origin were highly sensitive (IC50 values of 0.86-1.98 μg/mL) to gossypol. The antiproliferative action of gossypol was not restricted to reproductive **cancers**, as nonreproductive **cancer** cell lines were also equally sensitive (IC50 values of 0.69-3.55 μg/mL). In addition, actively proliferating untransformed cells such as fibroblasts and PHA-activated lymphocytes were also sensitive (IC50 values of 0.87-2.51 μg/mL). (-)-Gossypol was 3.6-12.4 times more potent than (+)-gossypol and 1.48-2.65 times more potent than (±)-gossypol. The most sensitive indicator of gossypol action was a decrease in DNA synthesis, followed by inhibition of protein synthesis and uptake of rhodamine-123 by mitochondria, as tested in an ovarian **cancer** cell line (OVCA 433) and a fibroblast line (Hs27). Gossypol possesses a general nonselective antiproliferative action toward human cells in vitro. Further, the pharmacol. activity of gossypol as an antiproliferative agent is primarily attributable to its (-) isomer, which is also the active isomer as a contraceptive.

CC 1-6 (Pharmacology)
Section cross-reference(s): 2

ST gossypol gonadal **cancer**; cell proliferation gossypol isomer

IT **Neoplasm inhibitors**
(gossypol isomer as, for gonadal cells)

IT 303-45-7, (±)-Gossypol 20300-26-9, (+)-Gossypol **90141-22-3**, (-)-Gossypol
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES

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L21 (       495)SEA FILE=MEDLINE ABB=ON  PLU=ON  L19/MAJ
L22 (    365762)SEA FILE=MEDLINE ABB=ON  PLU=ON  L20/MAJ
L23 (        17)SEA FILE=MEDLINE ABB=ON  PLU=ON  L21 AND L22
L24 (        17)SEA FILE=MEDLINE ABB=ON  PLU=ON  L23 AND PY<=2004
L25           4 SEA FILE=MEDLINE ABB=ON  PLU=ON  L24 AND PY<=1990
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/MAJ here and in EMBASE indicates a "major descriptor"; i.e. the main point of the article

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 substance identification.

=> d que l11
L1             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  "(-)-GOSSYPOL"/CN
L2          1036 SEA FILE=EMBASE ABB=ON  PLU=ON  GOSSYPOL/CT OR L1
L3           838 SEA FILE=EMBASE ABB=ON  PLU=ON  L2/MAJ
L5        564986 SEA FILE=EMBASE ABB=ON  PLU=ON  "ANTINEOPLASTIC AGENT"+NT/CT
L6        372774 SEA FILE=EMBASE ABB=ON  PLU=ON  L5/MAJ
L7            77 SEA FILE=EMBASE ABB=ON  PLU=ON  L3 AND L6
L8       1241999 SEA FILE=EMBASE ABB=ON  PLU=ON  NEOPLASM+NT/CT
L9       1041317 SEA FILE=EMBASE ABB=ON  PLU=ON  L8/MAJ
L10           14 SEA FILE=EMBASE ABB=ON  PLU=ON  L7 AND L9
L11           11 SEA FILE=EMBASE ABB=ON  PLU=ON  L10 AND PY<=1990


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L26           19 DUP REM L25 L11 L18 (2 DUPLICATES REMOVED)

=> d ibib abs hitind l26 1-19

L26  ANSWER 1 OF 19     MEDLINE on STN                    DUPLICATE 1
ACCESSION NUMBER:   90294807     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 2193225
TITLE:              Biochemical correlates of the antitumor and
                    antimitochondrial properties of gossypol enantiomers.
AUTHOR:             Benz C C; Keniry M A; Ford J M; Townsend A J; Cox F W;
                    Palayoor S; Matlin S A; Hait W N; Cowan K H
CORPORATE SOURCE:   Cancer Research Institute, University of California, San
                    Francisco 94143.
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CONTRACT NUMBER: CA46966 (NCI)
SOURCE: Molecular pharmacology, **(1990 Jun)** 37 (6) 840-7.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199008
ENTRY DATE: Entered STN: 19900907
Last Updated on STN: 19980206
Entered Medline: 19900801

AB Racemic gossypol has been shown to have antitumor properties that may be due to its ability to uncouple tumor mitochondria or to its inhibitory effects on a variety of nonmitochondrial enzymes. We have studied the antimitochondrial and enzyme-inhibiting properties of gossypol in human carcinoma cell lines of breast (MCF-7, T47-D), ovarian (OVCAR-3) colon (HCT-8), and pancreatic (MiaPaCa) origin by comparing the effects of its purified (+)- and (-)-enantiomers. (-)-Gossypol shows up to 10-fold greater antiproliferative activity than (+)-gossypol in the cancer cell lines and in normal hematopoietic stem cells grown in vitro, with IC50 values ranging from 1.5 to 4.0 microM for the cancer cells and from 10 to 20 microM for the human marrow stem cells. As well, multidrug-resistant MCF/Adr cells appear more resistant to (-)-gossypol than their parental cell line. Electron microscopy indicates that the earliest ultrastructural change in tumor cells exposed to a cytotoxic (10 microM) concentration of (-)-gossypol is the selective destruction of their mitochondria. Consistent with this observation, 31P magnetic resonance spectroscopy detects pronounced changes in tumor cell high energy phosphate metabolism within 24 hr of (-)-gossypol treatment, manifest by 1.6- to greater than 50-fold differential reductions in the intracellular ratios of ATP/Pi, relative to (+)-gossypol-treated cell lines; the magnitude of these antimitochondrial effects correlates with the antiproliferative activity of (-)-gossypol. Northern blot RNA analyses suggest that treatment with a 5-10 microM dose of (-)-gossypol induces a transient increase in the expression of heat shock gene products, particularly hsp-70 transcripts. The mean 5-fold increase in (-)-gossypol-induced hsp-70 mRNA appears coincident with a comparable heat-stimulated increase in transcript levels, as compared with control or (+)-gossypol-treated cells. The enzyme-inhibiting properties of gossypol enantiomers were compared in cell-free assays measuring glutathione-S-transferase-alpha, -mu, and pi activities, calmodulin stimulation of cyclic nucleotide phosphodiesterase, and protein kinase C activity. Both enantiomers are near equivalent antagonists of calmodulin stimulation and protein kinase C activity, exceeding the potency of known inhibitors such as phenothiazines by as much as 50-fold. In contrast, (-)-gossypol is a 3-fold more potent inhibitor of glutathione-S-transferase-alpha and -pi isozyme activity, resulting in IC50 values of 1.6 and 7.0 microM, respectively, for these two isozymes.(ABSTRACT TRUNCATED AT 400 WORDS)

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

***Antineoplastic Agents**
Calmodulin: PD, pharmacology
Glutathione Transferase: ME, metabolism
***Gossypol: PD, pharmacology**
Heat-Shock Proteins: BI, biosynthesis
Heat-Shock Proteins: GE, genetics
Isoenzymes: ME, metabolism
*Mitochondria: DE, drug effects